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Comparative effect of different corticosteroids in severe community-acquired pneumonia: a network meta-analysis

Liangdong Zhu[1†], Jia Zeng[2†], Hui Li[1], Keyu Li[1] and Xia Chen[3*]

Abstract

Background and objectives Severe community-acquired pneumonia (CAP) is a potentially fatal pulmonary disease. Although studies have investigated the efficacy and safety of corticosteroids for severe CAP, the results remain inconsistent. Moreover, there is a lack of sufficient evidence to rank the effects of different types of corticosteroids. The aim of this study is to elucidate the effects of different corticosteroids in patients with severe CAP.

Methods We searched PubMed, Embase, Cochrane Library, and Web of Science comprehensively, encompassing all publications with a search deadline of March 31, 2024. Only randomized controlled trials (RCTs) involving the treatment of severe CAP with corticosteroids were included. The primary efficacy outcome was all-cause mortality, secondary efficacy outcome was mechanical ventilation (MV), and safety outcome was the incidence of serious adverse events (SAEs).

Results A total of 11 studies, involving 2042 participants, compared four corticosteroids (hydrocortisone, dexamethasone, prednisolone, methylprednisolone). The included trials were all corticosteroid versus placebo comparisons, resulting in a star-shaped network. Among the four corticosteroids, only hydrocortisone was significantly more effective at reducing mortality than placebo (RR, 0.35; 95% CrI, 0.14–0.64). Additionally, hydrocortisone reduced the need for MV (RR, 0.73; 95% CrI, 0.51–0.93). Furthermore, subgroup analysis indicated that low-to-moderate doses, short-course corticosteroids are associated with a reduction in both mortality and the need for MV.

Conclusion In the evaluated corticosteroid regimen, hydrocortisone might be an effective measure to reduce all-cause mortality in patients with severe CAP.

Clinical trial number The present study is a meta-analysis and literature review, therefore clinical trial number is not applicable.

Keywords Hydrocortisone, Pneumonia, Network meta-analysis

†Liangdong Zhu and Jia Zeng contributed equally to this work as first authors.

*Correspondence:
Xia Chen
zld199212@163.com

[1]The First Hospital of Changsha, Changsha, China
[2]National Respiratory Center of the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China
[3]The First Affiliated Hospital of Hunan University of Medicine, Huaihua, China

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Introduction

Severe community-acquired pneumonia (CAP) constitutes a potentially fatal pulmonary infection that significantly affects healthcare resources and has high morbidity and mortality [1, 2]. Dysregulation of pulmonary and systemic inflammatory responses can lead to extensive tissue damage, progression to sepsis, acute respiratory distress syndrome (ARDS), and multiple organ failure. Corticosteroids exert anti-inflammatory effects by inhibiting the excessive production of inflammatory mediators, which may reduce the risk of severe lung injury, ARDS, multiple organ failure, and subsequent death [3, 4].

The efficacy and safety of corticosteroids in treating severe CAP have been investigated in randomized controlled trials (RCTs); however, the results remain controversial [5–7]. The Santeon-CAP trial demonstrated that dexamethasone reduced the ICU admission rate for patients in the severe CAP subgroup, although it did not improve 30-day mortality [7]. Conversely, the ESCAPe trial showed that low-dose methylprednisolone shortened the length of mechanical ventilation (MV) required for patients but did not yield positive results in terms of 60-day mortality [6]. However, the CAPE COD trial results indicated that hydrocortisone significantly lowered the 28-day mortality among patients with severe CAP in the ICU [5].

Previous studies have investigated the effects of corticosteroids on severe CAP, but the data and results have been conflicting, particularly regarding mortality outcomes [8–10]. Several meta-analyses have demonstrated a correlation between corticosteroid use and decreased mortality, as well as reduced requirements for MV among these patients [11]. However, meta-analyses conducted by Briel and colleagues suggested that corticosteroids failed to improve survival rates in severe CAP [10]. In contrast, a systematic review by Huang and colleagues found that treatment with prednisolone or methylprednisolone reduced mortality, whereas hydrocortisone did not exhibit such an effect [12]. However, recent meta-analyses have suggested that only hydrocortisone can reduce mortality [8]. The central challenges remain in identifying the optimal types, dosages, and durations of corticosteroid therapy [13, 14]. Moreover, the scarcity of direct comparative RCTs assessing the effects of corticosteroids complicates these findings. Consequently, we conducted a network meta-analysis to evaluate the efficacy and safety of different types of corticosteroids for severe CAP.

Materials and methods

Search strategy and data sources

We searched PubMed, Embase, Cochrane Library, and Web of Science comprehensively, encompassing all publications with a search deadline of March 31, 2024, with no language restrictions, using a combination of keywords and MeSH terms related to community-acquired pneumonia and corticosteroids (including hydrocortisone, prednisolone, methylprednisolone, and dexamethasone). The search strategy was developed by an experienced researcher and is detailed in Table S1. In addition, we conducted a manual search of the references cited in the included studies to identify any other potentially relevant research. This study was registered in PROSPERO (CRD42024544342) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

Study selection

The inclusion criteria for this study were as follows: (1) Population: Severe CAP; (2) Intervention: Corticosteroids, including hydrocortisone, prednisolone, methylprednisolone, and dexamethasone, were administered at dosages designed to distinguish between low-to-moderate and high doses. Low-to-moderate doses were defined as <1 mg/kg per day of methylprednisolone or <80 mg per day of methylprednisolone or its equivalent, whereas doses equal to or exceeding either threshold were classified as high doses [16, 17]; (3) Comparison: Placebo; (4) Outcomes: The primary efficacy outcome was all-cause mortality, the secondary efficacy outcome was MV, and the safety outcome was the incidence of SAEs; and (5) study design: RCTs. Severe CAP was defined as CAP that required admission to the ICU or met the criteria established by the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA), or PaO2/FiO2 <300, or pneumonia severity index score $\geq$ IV [18, 19]. Only data from the subgroup with severe CAP were included if the studies enrolled patients with different severity levels of CAP. In additionally, we excluded non-RCTs, duplicate publications, conference reports, and studies with incomplete data.

Two authors screened the study titles and abstracts to establish eligibility and conducted rigorous preliminary selection. Subsequently, the full text was reviewed based on the inclusion criteria, leading to further exclusion. Discrepancies were resolved by consulting with a third independent researcher.

Data extraction

Two authors extracted pertinent demographic data and study outcomes, including all-cause mortality, need for MV, and SAEs. Additionally, we categorized the included trials based on the treatment dosage and duration.

Quality assessment

We used the Cochrane Collaboration tool to assess the risk of bias in all RCTs [20]. Two researchers

independently completed this assessment and all discrepancies were resolved through consensus-based discussions.

Statistical analysis

This study used a network meta-analysis based on a Bayesian framework. All available direct and indirect comparison data were included in a hierarchical Bayesian model, analyzed using the gemtc package (V.1.0.2) in R software (V.4.4.1) [21]. Risk ratios (RR) and 95% confidence intervals (CrI) were used to estimate effect sizes. A statistically significant difference between the two interventions was indicated when the 95% CrI did not include 1. The pooled analysis was conducted using a random-effects model to account for heterogeneity between individual studies and to enhance the generalizability of the analysis. We used the heterogeneity index (I^2) to assess the heterogeneity between studies, where $I^2 > 50\%$ indicates significant heterogeneity. If the network plot shows a closed loop, the network heterogeneity between direct and indirect comparisons within the loop should be assessed. We used the node-splitting model to assess the statistical inconsistency between direct and indirect comparisons. For all outcomes, the network meta-analysis was performed using the Markov Chain Monte Carlo (MCMC) method for inference. Four independent MCMC chains were run with 10,000 adaptation iterations to stabilize sampling, followed by 50,000 sampling iterations per chain, applying a thinning interval of 10 to reduce autocorrelation. During the analysis, Stata software (V.15.0 MP) was used to assess publication bias, and a comparison-adjusted funnel plot was used for further validation, where the symmetry of the funnel plot indicates minimal bias. Additionally, we calculated the surface under the cumulative ranking curve (SUCRA) to assess the ranking probabilities of different therapeutic drugs, with higher SUCRA values indicating better relative effects of the intervention.

Credibility of the evidence

Using the online Confidence in Network Meta-Analysis (CINeMA) tool for network meta-analysis, researchers assessed the quality of evidence across six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Each domain was rated as "major concerns," "some concerns," or "no concerns," and the overall confidence in the evidence was then determined based on an integrated assessment of these domains [22].

Results

Eligible studies and characteristics

The search generated 4654 publications, of which 11 RCTs were ultimately included for analysis in this study [5–7, 14, 23–28]. The flowchart for selecting the studies is summarized in Fig. 1. Among these 11 trials, 7 were multicenter studies, and 4 were single-center studies, involving 2042 patients with sample sizes ranging from 30 to 795. The studies utilized different treatments with corticosteroids: hydrocortisone was used in 6 trials, methylprednisolone in 3, dexamethasone in 1, and prednisolone in 1. Importantly, the control groups in all the studies used placebos. The characteristics of all the included trials are detailed in Table S2 and Table S3.

Quality assessment

A detailed description of the quality assessments for the included RCTs is provided (Fig. S1). The overall risk of bias was low in most studies.

Network graph

The trial network structure shows the trial network for each outcome (Fig. 2). As no closed loop is formed in the comparisons between corticosteroids and placebo, the network appears as a 'star-shaped' structure. Each node (circle) represents a specific treatment. The nodes are connected by solid deep blue lines, with the width of the lines reflecting the number of studies in each comparison, and the size of the nodes is proportional to the total sample size of each treatment comparison.

Primary outcome

Of the 11 trials included, the primary outcome of all-cause mortality was pooled across 2042 participants, comparing hydrocortisone, dexamethasone, prednisolone, methylprednisolone, and placebo. The network meta-analysis revealed that hydrocortisone was significantly more effective in reducing mortality than placebo (RR, 0.35; 95% CrI, 0.14–0.64). No significant differences were observed between dexamethasone, prednisolone, methylprednisolone, and placebo. Additionally, we combined individual head-to-head studies to evaluate the differences in efficacy between corticosteroids. No evidence was found to suggest that any corticosteroid treatment was superior to others. These data for the primary outcomes are summarized in the league table (Fig. 3).

In terms of mortality for severe CAP, hydrocortisone appears to be the most effective treatment, as indicated by a SUCRA value of 88.7%. Dexamethasone and methylprednisolone yielded SUCRA values of 56.9% and 41.9%, respectively, while prednisolone was found to be the least beneficial, with a SUCRA of 36.3% (Fig. 3). We did not observe significant overall heterogeneity in mortality (heterogeneity test results, $I^2 = 7\%$).

Secondary outcome

Seven trials involving a total of 843 participants reported on the outcomes of MV. Hydrocortisone was associated

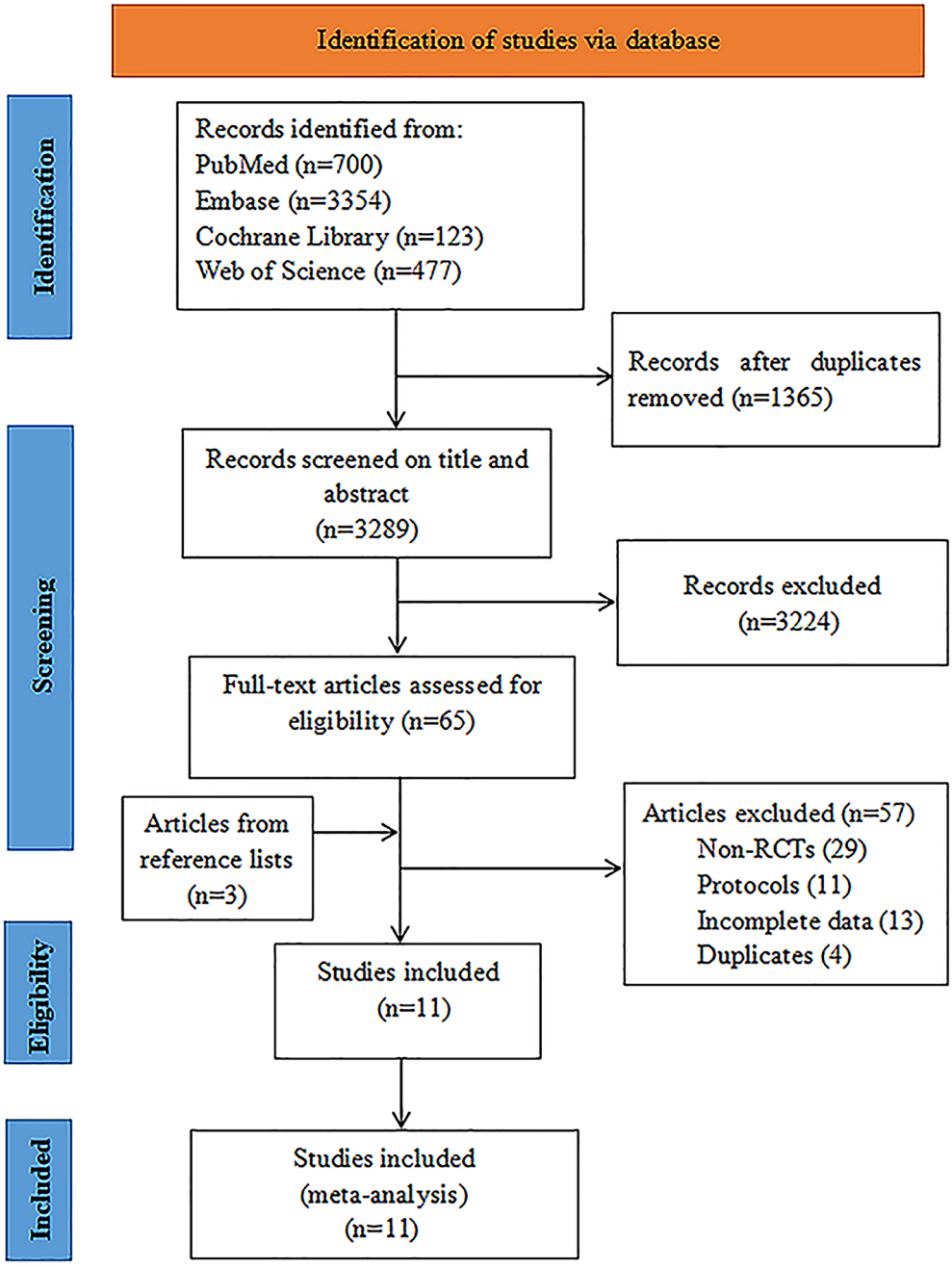


Fig. 1 Flowchart of the selection process

with a significant reduction in the need for MV (RR, 0.73; 95% CrI, 0.51–0.93). However, no evidence was found to suggest that hydrocortisone was superior to methylprednisolone. We did not observe significant overall heterogeneity in MV (heterogeneity test results, I^2 = 18%). These data are summarized in the league table (Fig. S2). Hydrocortisone is considered the best treatment strategy for patients with severe CAP, as evidenced by an SUCRA value of 91.9%, and methylprednisolone has an SUCRA value of 48.7%.

Six studies involving a total of 1705 participants, reported on SAEs. No statistically significant differences were observed between hydrocortisone, methylprednisolone, and placebo. Hydrocortisone reduced the risk of SAEs (RR, 0.51; 95% CrI, 0.18–0.95). We did not observe significant overall heterogeneity (heterogeneity test results, I^2 = 16%). These data are summarized in the league table (Fig. S2). For SAEs, hydrocortisone demonstrated the highest SUCRA value of 96.1%, followed by methylprednisolone at 31.2%, and placebo at 22.7%.

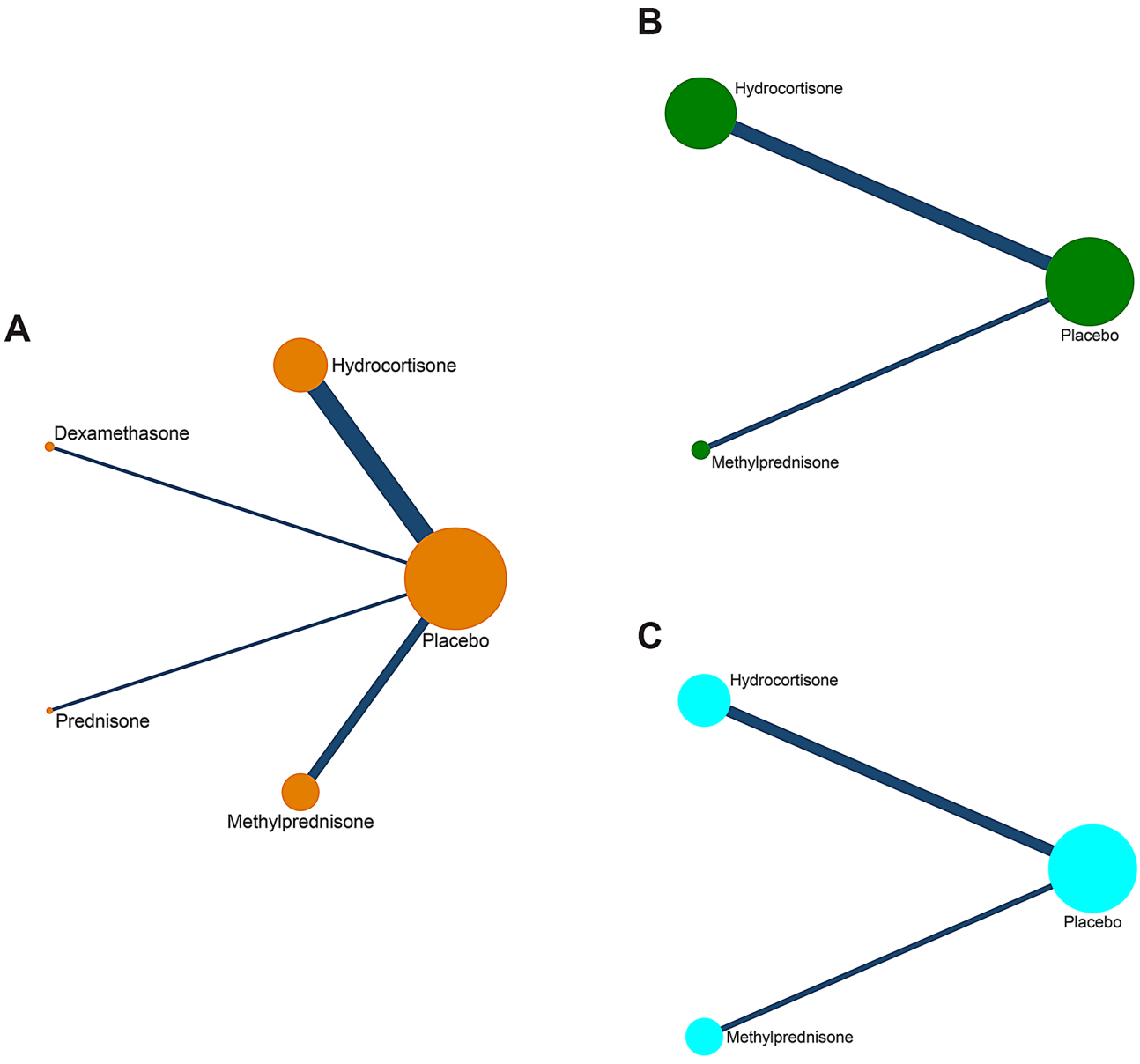
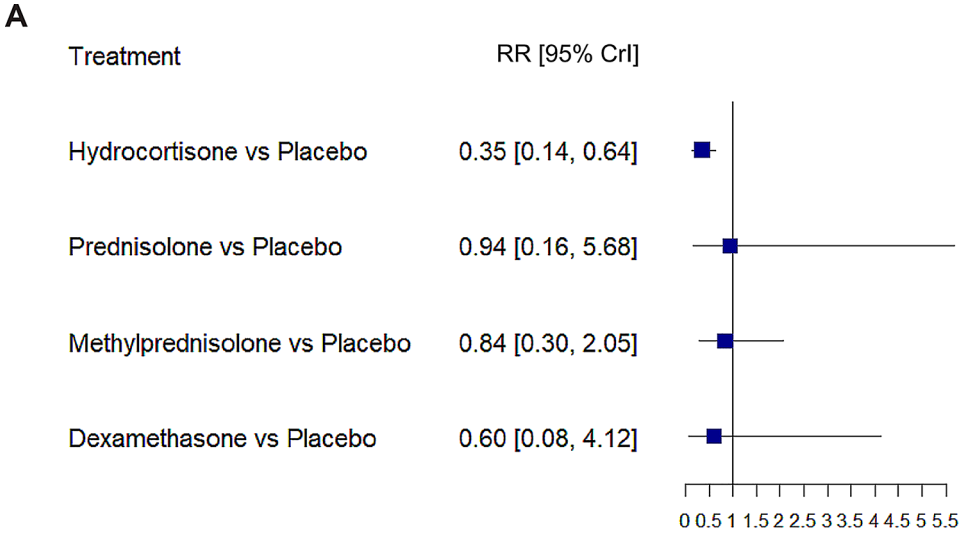


Fig. 2 Network graph. (**A**) The network plot of all-cause mortality. (**B**) The network plot of MV. (**C**) The network plot of SAEs

Subgroup analyses

Subgroup analysis indicated that low-to-moderate doses corticosteroids were associated with reduced mortality compared to placebo (RR, 0.50; 95% CrI, 0.23–0.85). No significant overall heterogeneity was observed (heterogeneity test results, I^2 = 11%). In addition, patients receiving low-to-moderate doses of corticosteroids showed a significant reduction in the need for MV compared to those who received a placebo (RR, 0.50; 95% CrI, 0.29–0.78). No significant overall heterogeneity was observed (heterogeneity test results, I^2 = 0%). Furthermore, no significant differences were observed in the incidence of severe adverse events (SAEs) between high-dose corticosteroids, low-to-moderate doses corticosteroids, and placebo (Fig. 4). The survival rate of patients who received short-term therapy was significantly higher than placebo (RR, 0.40; 95% CI, 0.20–0.72). No significant overall heterogeneity was observed (heterogeneity test results, I^2 = 9%). For the outcome of MV, short-course corticosteroids proved beneficial in reducing the need for MV (RR, 0.44; 95% CrI, 0.26–0.77). No significant overall heterogeneity was observed (heterogeneity test results, I^2 = 13%). Additionally, there was no substantial difference in SAEs between patients treated with short and long-course treatments (Fig. 4). These data are summarized in the league table (Figs. S3, S4, and S5).



B

Hydrocortisone				
0.37 (0.04, 2.22)	Prednisolone			
0.43 (0.11, 1.24)	1.13 (0.15, 9.04)	Methylprednisolone		
0.58 (0.06, 4.45)	1.57 (0.11, 24.13)	1.39 (0.16, 12.77)	Dexamethasone	
0.35 (0.14, 0.64)	0.94 (0.16, 5.68)	0.84 (0.30, 2.05)	0.60 (0.08, 4.12)	Placebo

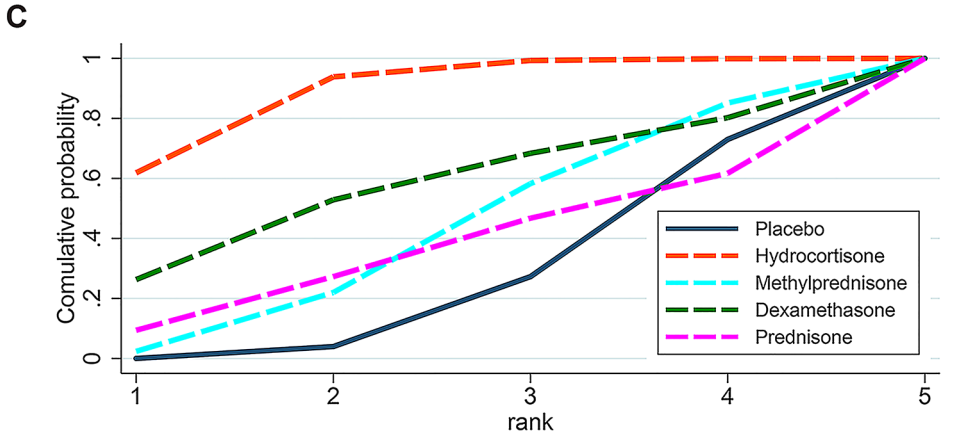


Fig. 3 Network meta-analysis results for all-cause mortality. (**A**) A forest plot comparing all corticosteroid treatments with placebo. (**B**) The league table displays the network meta-analysis estimates for all treatment comparisons, with relative risk (RR) and 95% confidence intervals. Items in bold indicate statistical significance. (**C**) A SUCRA-based cumulative probability graph for all-cause mortality

Credibility of the evidence

The evidence credibility was evaluated using the CINeMA tool. For comparisons regarding all-cause mortality, MV, and SAEs, the evidence credibility was rated from very low to low. The assessment of evidence certainty was largely driven by serious concerns about incoherence, heterogeneity, or imprecision in several comparisons [Tables S4, S5, and S6].

Publication bias

We assessed publication bias only for the primary outcomes. Due to an insufficient number of studies, publication bias for the secondary outcomes was not evaluated.

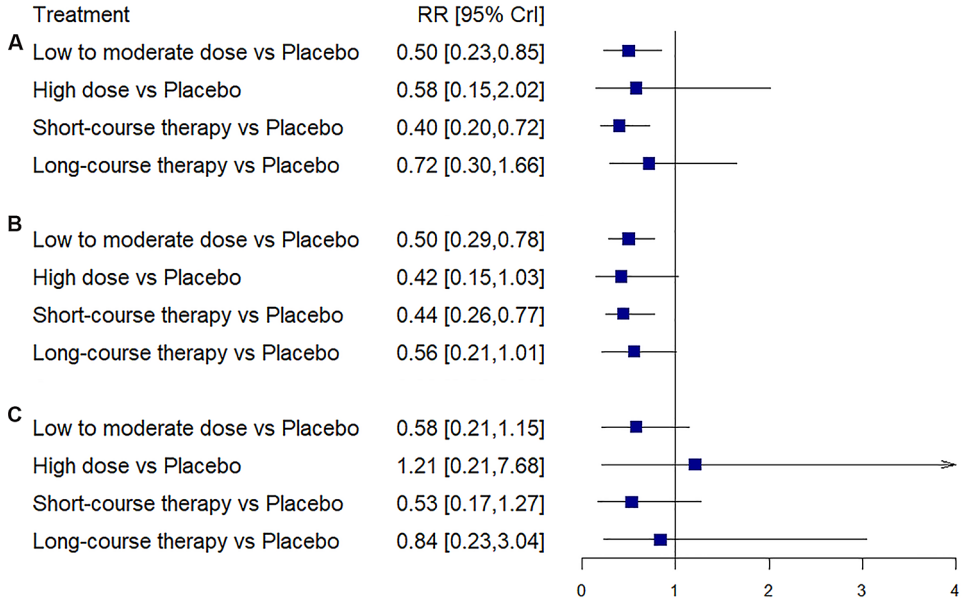


Fig. 4 The forest plot of subgroup analyses. (**A**) The forest plot for all-cause mortality. (**B**) The forest plot for MV. (**C**) The forest plot for SAEs. MV, mechanical ventilation; SAEs, serious adverse events

The comparison-adjusted funnel plot did not exhibit significant asymmetry, and all study comparisons fell within the 95% CrI of the funnel plot's sloped lines (Fig. S6). Therefore, no evidence of publication bias was found for all-cause mortality in the included studies.

Discussion

In this network meta-analysis of 11 RCTs involving 2042 patients with severe CAP, we aimed to determine the optimal corticosteroid regimen. Hydrocortisone was associated with a statistically significant reduction in all-cause mortality compared with placebo (RR, 0.35; 95% CrI, 0.14–0.64). While this finding is statistically significant, its clinical relevance requires further consideration. Traditionally, overreliance on p-values and SUCRA rankings may lead to overlooking the practical implications of therapeutic interventions in clinical settings. SUCRA values reflect relative rankings rather than absolute clinical benefit and should be interpreted with caution. To address these, Horita et al. recently proposed a framework for the minimal clinically important difference (MCID), which is applicable to effect sizes such as RR [29]. According to this framework, an RR of 0.35 is not only statistically significant but also clinically meaningful, demonstrating a substantial mortality benefit. Further comparative analysis suggested that hydrocortisone may outperform methylprednisolone, dexamethasone, and prednisolone in reducing mortality. Additionally, our results indicate that patients may benefit more from corticosteroids administered in low-to-moderate doses and over short courses.

Previous direct meta-analyses have investigated the effect of corticosteroids on severe CAP, but the results remain inconclusive [8, 9, 12]. Our network meta-analysis revealed that unlike other corticosteroids, hydrocortisone not only significantly reduced mortality, but also reduced the need for MV. These findings underscore the distinct advantages of hydrocortisone in improving patient prognosis. Importantly, owing to the absence of direct comparative RCTs between different corticosteroids, our analysis provides critical insights suggesting that hydrocortisone may be more effective in reducing mortality and MV. Evidence credibility was rated as very low to low for outcomes including all-cause mortality, MV, and SAEs, primarily due to concerns regarding incoherence, heterogeneity, and imprecision. These limitations warrant cautious interpretation of hydrocortisone's potential benefits and highlight the need for well-designed, adequately powered head-to-head RCTs to validate these findings.

Hydrocortisone is a low-potency, short-acting corticosteroid that offers distinct clinical advantages over more potent, long-acting agents such as prednisolone, methylprednisolone, and dexamethasone [30]. The pathogenesis of severe CAP typically involves a hyperinflammatory response, characterized by a cytokine storm, which leads to alveolar epithelial damage and impaired oxygen exchange [31]. Hydrocortisone inhibits the NF-κB signaling pathway mediated by glucocorticoid receptors, selectively reducing the release of pro-inflammatory cytokines, thereby alleviating pulmonary tissue damage. By providing moderate immunomodulation, it prevents excessive immunosuppression and lowers the risk

of secondary infections [32]. Additionally, the short half-life of hydrocortisone allows for dynamic dosage adjustments according to disease progression, reducing adverse effects such as hyperglycemia and muscle atrophy. This makes it especially suitable for critically ill patients who require meticulous management [30]. Hydrocortisone does not require hepatic metabolic activation, making it suitable for severe CAP patients with impaired liver function, offering higher safety and more predictable pharmacological responses. Notably, hydrocortisone has dual glucocorticoid and mineralocorticoid activity, which enables it to activate the renin-angiotensin-aldosterone system, providing crucial hemodynamic support while reducing reliance on vasopressor agents [3, 33]. In summary, hydrocortisone achieves the optimal balance between efficacy and safety in the treatment of severe CAP and holds promise as an ideal option for personalized therapy in severe pneumonia.

In addition to focusing on the clinical benefits of corticosteroids, physicians should also be aware of their potential side effects [34]. This study evaluated SAEs associated with corticosteroid use in severe CAP, including opportunistic infections, cardiac events, neuropsychiatric symptoms, acute renal failure, gastrointestinal bleeding, and hyperglycemia. The results indicate that corticosteroids do not significantly increase the risk of SAEs, which is consistent with previous research [8, 9]. However, larger, well-designed studies are warranted to confirm their long-term safety profile.

Guidelines from the European Society of Intensive Care Medicine recommend the use of corticosteroids for moderate to severe ARDS within 14 days of onset [35]. However, the evidence of severe CAP with corticosteroids remains complex and contradictory [3, 36]. The CAPE COD trial notably supported corticosteroid use and demonstrated that hydrocortisone significantly reduces mortality. Despite these findings, determining the optimal type, dosage, and duration of corticosteroids still unresolved [13, 37]. Our analysis assessed the effects of high and low-to-moderate doses and long and short courses of treatment on mortality, MV, and SAEs. The aggregated results suggest that low-to-moderate doses and short courses of treatment are more effective in reducing mortality. These observations provide a preliminary basis for therapeutic refinement and underscore the need for additional RCTs to develop definitive guidelines.

Previous studies have primarily relied on direct meta-analyses, which can provide limited insight into the comparative effectiveness of different treatments. To overcome this limitation, this study employed network meta-analysis to enhance the precision of the results and enable a more comprehensive comparison of the efficacy of different corticosteroids. Despite these advances, our study had several limitations. First, the included RCTs varied in the diagnostic criteria for severe CAP and the definition and reporting of SAEs, which may have caused heterogeneity between the studies. Additionally, although corticosteroids may improve clinical outcomes in patients with severe CAP, their immunosuppressive effects could theoretically increase the risk of secondary infections and antibiotic resistance. However, none of the included studies in our meta-analysis provided specific data on the incidence of antibiotic-resistant pathogens or secondary bacterial or fungal infections. This lack of data represents an important limitation, as the potential for increased susceptibility to nosocomial or opportunistic infections could offset the benefits of corticosteroid therapy. Future trials should incorporate comprehensive microbiological surveillance to assess this risk more precisely and guide safer clinical decision-making. Moreover, due to the limited number of qualifying RCTs, it was not feasible to conduct sensitivity analyses without compromising the integrity of the network structure, which, in turn, limits the ability to draw definitive conclusions regarding the optimal dosages and treatment durations for various corticosteroids. Finally, the generalizability of our findings may be limited by heterogeneity across study populations, including variability in comorbidities, ICU admission status. Whether hydrocortisone provides comparable benefit across these diverse clinical subgroups remains uncertain and should be explored in future stratified analyses or individual patient data meta-analyses.

In summary, our study indicates that hydrocortisone significantly reduced mortality, whereas methylprednisolone, dexamethasone, and prednisolone did not exhibit the same effect. Furthermore, we confirmed the benefits of low-to-moderate doses and short-course corticosteroid therapy. While these findings may help guide clinical decision-making, they are not yet robust enough to warrant immediate changes to current treatment guidelines. To establish the optimal corticosteroid regimen, especially regarding the choice of agent, dose, and duration, further large-scale, high-quality randomized controlled trials are essential. Future research should particularly focus on direct head-to-head comparisons between hydrocortisone and other corticosteroids, such as methylprednisolone, to clarify their relative efficacy and safety profiles, and support the development of more precise, evidence-based treatment strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03679-w.

Supplementary Material 1

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Not applicable.

Author contributions
Liangdong Zhu and Jia Zeng, wrote the main manuscript text and Liangdong Zhu prepared figures 1-4. All authors reviewed the manuscript.

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Data availability
The data analyzed in the present manuscript are available upon reasonable request. Researchers who wish to access the raw data may contact Xia Chen at zld199212@163.com. Access will be granted upon reasonable request and in accordance with relevant data-sharing policies.

Declarations

Ethics approval and consent to participate
The present study is a meta-analysis and literature review, therefore ethics approval and consent to participate are not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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